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Surgery for constipation: systematic review and practice recommendations

Results I: Colonic resection

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Abstract

Aim To assess the outcomes of colectomy in adults with chronic constipation (CC).

Method Standardised methods and reporting of benefits and harms were used for all CapaCiTY reviews that closely adhered to PRISMA 2016 guidance. Main conclusions were presented as summary evidence statements (SES) with a summative Oxford Centre for Evidence-Based Medicine (2009) level.

Results Forty articles were identified, providing data on outcomes in 2045 patients. Evidence was derived almost exclusively from observational studies, the majority of which concerned colectomy and ileorectal anastomosis (CIRA) rather than other procedural variations. Average length of stay (LOS) ranged between 7–15 days. Although inconsistent, laparoscopic surgery may be associated with longer mean operating times (210 *vs* 167 min) and modest decreases in LOS (10–8 days). Complications occurred in approximately 24%

of patients. Six (0.4%) procedure-related deaths were observed. Recurrent episodes of small bowel obstruction occurred in about 15% (95%CI: 10–21%) of patients in the long-term, with significant burden of re-hospitalisation and frequent recourse to surgery. Most patients reported a satisfactory or good outcome after colectomy but negative long-term functional outcomes persist in a minority of patients. The influence of resection extent, anastomotic configuration and method of access on complication rates remains uncertain. Available evidence weakly supports selection of patients with an isolated slow-transit phenotype.

Conclusion Colectomy for CC may benefit some patients but at the cost of substantial short- and long-term morbidity. Current evidence is insufficient to guide patient or procedural selection.

Keywords Constipation, colectomy, ileorectal, slow-transit

Introduction

Background and procedural variations

The concept of resection of the colon to treat constipation originates more than a century ago [1]. Modern surgical approaches mostly continue in the historical practice of removing the whole colon with anastomosis of the terminal ileum to the upper rectum (or very distal sigmoid) usually at the level of the sacral promontory. Usually termed colectomy and ileorectal anastomosis (CIRA), the procedure is also sometimes described as colectomy with ileoproctostomy. Total

colectomy is not favoured by all surgeons and other less radical colonic resections may also be employed. The simplest variation is to perform a subtotal colectomy and ileosigmoid anastomosis (SCISA) but an increasingly popular choice is subtotal colectomy with sparing of the caecum and thence caecorectal anastomosis (SCCRA). Since this is not a common procedure in routine colorectal surgical practice, it merits some background description. First described by Ogilvie (1931), retention of the ileocaecal junction has the theoretical advantage of preservation of absorptive functions (bile, vitamin B12 and electrolytes) and thus perhaps reduced diarrhoea. No standard technique exists for creating a CRA. The general principle involves colonic mobilization followed by ligation of all vascular pedicles except the ileocolic branches. In the technique proposed by

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Lillehei and Wangenstein (1955) a 180° rotation of the remaining mesentery from the right to the left is performed to place the caecum in the left iliac fossa, with apex cephalad. During the rotation the remaining mesocolon passes over the aorta, and it is sutured to the mesorectum and to the third portion of the duodenum to avoid internal hernia or intestinal obstruction, which may complicate such technique. Deloyers (1963) proposed a variation of this technique in which there is a craniocaudal rotation of the caecum to allow a pelvic isoperistaltic CRA (IPSCCRA) but this required a retro-ileal tunnel and 180° torsion of the vascular pedicle which may result in ischemia or venous stasis. These difficulties have in part been mitigated by development of an antiperistaltic end-to-end caecorectal anastomosis (attributed to Sarli [2]) (APSCCRA) which avoids the vascular problems due to the torsion of the pedicle, obviates the need to tailor the caecum and lowers the risk of intestinal obstruction due to the rotation of the mesocolon in front of the aorta.

Scope

Procedures considered beyond the scope of systematic review [1–18] were:

- 1 Total colonic and rectal excision (proctocolectomy). These procedures have been variously employed for chronic constipation with or without ileal pouch

formation in small numbers of patients and usually as a salvage after failed colectomy;

- 2 Subtotal colectomy and modification of the rectal reservoir (modified Duhamel procedure; Jinling procedure);
- 3 Colonic exclusion and ileorectal anastomosis i.e. without resection.

Previous reviews

Narrative reviews focused on the outcome of colectomy for constipation have been published in 1996 [10], 1999 [11], and 2006 [12]. No previous systematic review was identified.

Summary of search results and study quality

The search yielded a total of 85 manuscripts for full text review (Fig. 1). From these, 40 articles published between 1988 and 2015 contributed to the systematic review, providing data on outcomes in a total of 2045 patients (range 20–144 patients per study) based on 39 defined patient cohorts (Table 1). A US nationwide dataset derived from hospital episode statistics was also included covering 2377 procedures coded as colectomy for constipation indications [19]. Specific exclusions after full-text review (and after exclusion of non-English language publications: $n = 10$) included 27 studies where the population sample was confirmed to be less

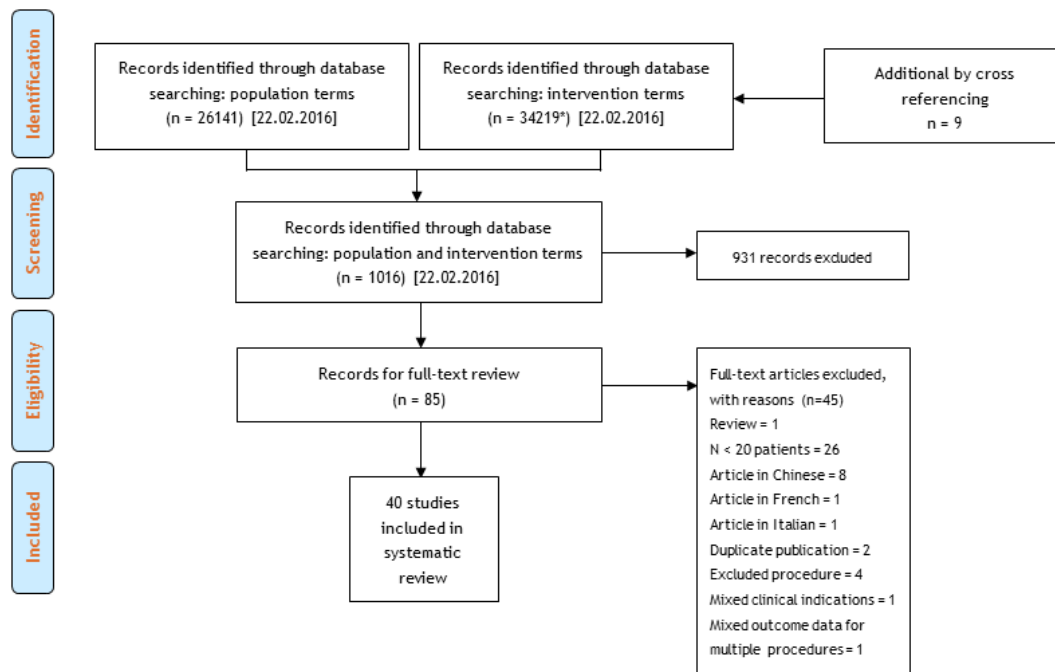


Figure 1 PRISMA diagram.

Table 1 All studies included in systematic review.

Author	Year	Centre	Country	Total N	FU*	Design	Level†
Kamm [23]	1988	St Marks, London	UK	44	> 12	RCS	IV
Vasilevsky [24]	1988	Mayo Clinic, MN	USA	52	46	RCS	IV
Yoshioka & Keighley [25]	1989	Birmingham	UK	40	36	RCS	IV
Pemberton [26]	1991	Mayo Clinic, MN	USA	36	36	PCS	IV
Piccirillo [27]	1995	Cleveland Clinic, FL	USA	54	27	RCS	IV
Redmond [21]	1995	John Hopkins, Baltimore	USA	34	90	PCH	IIB
de Graaf [28]	1996	Rotterdam	Netherlands	42	46	PCH	IV
Lubowski [29]	1996	Sydney	Australia	52	42	RCS	IV
Platell [30]	1996	Perth	Australia	96	60	RCS	IV
Pluta [31]	1996	Alberta	Canada	24	65	RCS	IV
Ghosh [32]	1996	Edinburgh	UK	21	96	RCS	IV
Nyam [33]	1997	Singapore	Singapore	74	56	PCH	IV
Ho [34]	1997	Singapore	Singapore	24	24	RCH	IV
You [35]	1998	Taiwan	China	40	24	PCS	IV
Bernini [36]	1998	Mayo Clinic, MN	USA	106	78	RCH	IV
Hasegawa [37]	1999	Birmingham	UK	61	84	RCH	IV
Fan [38]	2000	Taiwan	China	24	23	RCS	IV
Pikarsky [39]	2001	Cleveland Clinic, FL	USA	62	105	RCH	IV
Pikarsky [40]	2001	Cleveland Clinic, FL	USA	30	60	PCS	IV
Webster & Dayton [41]	2001	Cancun	Mexico	50	12	RCS	IV
Mollen [42]	2001	Bennekom	Netherlands	21	62	PCS	IV
Nylund [43]	2001	Goteburg	Sweden	40	132	PCS	IV
Lundin [44]	2002	Uppsala	Sweden	28	50	PCS	IV
Fitzharris [45]	2003	Mayo Clinic, MN	USA	75	47	RCS	IV
Hassan [46]	2006	Mayo Clinic, MN	USA	104	68	RCH	IV
Marchesi [47]	2007	Parma	Italy	23	72	PCS	IV
Zutshi [48]	2007	Cleveland Clinic, OH	USA	69	130	RCS	IV
Feng [22]	2008	Zhejiang	China	79	47	RCH	IIB
Hsiao [49]	2008	Taiwan	China	44	12	PCS	IV
Jiang [50]	2008	Whuhan	China	37	48	RCH	IV
Pinedo [51]	2009	Santiago	Chile	20	25	RCS	IV
Riss [52]	2009	Vienna	Austria	20	84	RCS	IV
Sohn [53]	2011	Soeul	Korea	37	41	RCS	IV
Xu LS [20]	2012	Harbin	China	64	32‡	RCT	IIB
Marchesi [54]	2012	Parma	Italy	30	12	CCS	IV
Wang [55]	2013	Zhejiang	China	124	12	RCH	IV
Reshef [56]	2013	Cleveland Clinic, OH	USA	144	43	RCH	IV
Li [57]	2014	Chongqing	China	72	64§	RCH	IV
Sun [58]	2015	Shanghai	China	48	36	RCH	IV
Total				2045	47¶		—
Dudekula [19]	2015	US nationwide sample	USA	2377**	12	RCH	IV

RCS, retrospective cohort study; PCS, prospective cohort study; RCT, randomised controlled trial; CCS, case control study.

*Mean follow up in months.

†Oxford CEBM [16].

‡Only 4 days blinded.

§For CIRA but 32 months for APSCCRA.

¶Median value of follow up.

**181 for state sample and 56 with 12 months pre & post-intervention.

than 20 patients, four studies of out of scope procedures, one study where data were considered duplicate [13], one where outcomes could not be segregated by

eligible procedure [14], and one where data for multiple clinical indications for colectomy were merged [15].

The general quality of studies was poor due to inadequate description of methods. The 40 included studies comprised: a single poor quality randomized trial (uncertain or high risk of bias in most domains) [20] (Oxford level IIB); one good quality prospective [21] and one retrospective cohort study [22] (level IIB); and 37 level IV studies (comprising 14 poor quality cohort studies, i.e. 'case comparison studies'; one poor quality case-control study with non-consecutive controls; eight prospective case series; and 14 retrospective case series). A general problem was the lack of prospectively defined follow up intervals. Patient follow up ranged from 12 months to 11 years (median 47 months) but this clearly varied greatly for individual patients within studies without defined follow up periods. Eleven studies derived from US centres, 11 from European centres, nine from Chinese centres with the remaining nine split across five countries.

Perioperative data

Perioperative data were reported by 37 studies (Table 2). Reporting of procedure duration was inconsistent but mean procedural duration ranged from approximately 2–4 h. Within this variation were trends of shorter operating times for open *vs* laparoscopic procedures (e.g. colectomy and ileorectal anastomosis (CIRA), median open: 167 min *vs* median laparoscopic: 210 min), as well as for subtotal procedures: median 135 min. The average length of stay (LOS) reported was 10.4 days, ranging from 7.0 to 15.5 days duration. However laparoscopic procedures consistently reported shorter lengths of stay e.g. the median LOS for open CIRA was 10.6 days compared to 8.1 days for laparoscopic CIRA. This evidence is supported by individual cohort comparisons [34,55] and in the single RCT where mean LOS was reduced from 9.7 to 7.6 days with laparoscopy [20].

Summary evidence statements: perioperative data

- 1 Length of stay after colectomy for constipation is 7–15 days, even in the modern era (level IV).
- 2 Laparoscopic surgery may be associated with longer operating times and modest decreases in length of stay (from 10 to 8 days), however there is considerable variation between studies (level IV).

Harms

Perioperative complications

Presented meta-analyses showed considerable heterogeneity of complications, not explained by procedure

or age of publication. The attentiveness to harm recording and the duration of recording were inconsistent and studies limited only to laparoscopic procedures are characterized by small numbers limiting scope for comparison with open procedures and no adjustment has been attempted for potential differences in the populations recruited into individual studies. Consequently estimates of harm provided are necessarily tentative.

Surgical morbidity remains a concern for all types of colectomy with total complication rates. A random effects meta-analysis estimated total complications to be 24.4% (95%CI: 17.8–31.7%); $I^2 = 88.1\%$ (Fig. 2), although findings were heterogeneous including individual study rates from 7% to 54% (Table 2). Aside from the incidence of anastomotic leaks and other more general complications (high even in some recent series from expert centres [56] and including six fatalities in 1568 patients: 0.4%) the incidence of prolonged post-operative ileus (POI) and early adhesional small bowel obstruction (SBO) are known to be disproportionately high for patients undergoing colectomy for slow-transit constipation when compared to other indications [17].

A random effects meta-analysis estimated early post-op POI/SBO to be 9.7% (95%CI: 5.7–14.6%); $I^2 = 87.9\%$ (Fig. 3), although findings were heterogeneous including individual study rates from 0% to 33%. Current findings are inconclusive as to whether laparoscopic or open surgery are safer: there is some suggestion however that the POI rate is lower in newer studies. Rates of further surgical intervention for POI in the perioperative period were similarly heterogeneous: 2.7% (95%CI: 1.0–5.0%) $I^2 = 64.3\%$, including study rates from 0% to 15%.

These data have been put into a broader context by the recent (2015) US national database study of 2377 colectomies for constipation between 1998–2011 [19], providing 60% of all subjects within the review. This study based on registered health episodes re-affirms a high rate of perioperative complications in a national sample (42.7% patients during index hospitalisation 30-day period), with the main contribution (27%) coming from "intestinal obstruction, ileus, nausea & vomiting".

Long-term adverse outcomes

Long-term rates of SBO reported by studies were heterogeneous: 15.2%, (95%CI: 10.2–20.9%) $I^2 = 85.5\%$, including study rates from 0% to 71% (Table 3; Fig. 4a). Re-operation rates (principally for SBO but also other severe ongoing functional

Table 2 Perioperative data by procedure.

Author	Year	N	Time	LOS	Bleed	Inf	Total cx	POI*	Re-op	Leak	Mort	
(a) Open colectomy and ileorectal anastomosis												
Pemberton [26]	1991	36	NR	12.0	NR	8.3	22.2	13.0	0	0	0	
Piccirillo [27]	1995	54	NR	7.0	NR	NR	NR	3.7	6	0	0	
Redmond [†] [21]	1995	37	NR	12.1	NR	NR	24	NR	NR	0	0	
Lubowski [29]	1996	52	NR	NR	NR	NR	NR	NR	NR	1.9	0	
Pluta [31]	1996	24	NR	NR	4.2	12.5	25	4.2	0	0	0	
Ghosh [32]	1996	21	NR	NR	NR	NR	NR	NR	NR	NK	0	
Nyam [33]	1997	74	NR	NR	NR	9.0	NR	12.0	0	0	0	
Ho [34]	1997	17	[‡]	10.6	NR	12.0	23.0	13.0	13.0	0	0	
Bernini [36]	1998	106	NR	NR	NR	NR	NR	23.0	14.1	0	0	
Fan [38]	2000	24	NR	10.0	NR	NR	NR	NR	0	0	0	
Pikarsky [40]	2001	30	NR	NR	NR	NR	NR	NR	NR	0	0	
Webster & Dayton [§] [41]	2001	55	NR	10.0	NR	NR	42.0	32.0	NR	4.0	0	
Mollen [42]	2001	21	NR	NR	NR	NR	33.0	19.0	9.5	0	0	
Nylund [43]	2001	40	NR	NR	5.0	7.5	20.0	5.0	5.0	0	0	
Fitzharris [45]	2003	75	NR	NR	NR	NR	NR	NR	NR	7	0.9	
Hassan [46]	2006	65	NR	NR	NR	NR	NR	NR	NR	0	0	
Jiang [50]	2008	21	140	15.5	NR	5.0	NR	NR	NR	0	0	
Sohn [53]	2011	37	203	12.0	NR	5.4	13.5	10.8	2.7	2.7	0	
Xu [20]	2012	32	145	9.7	NR	NR	NR	0	3.1	0	0	
Wang [55]	2013	68	190	11.0	0	7.4	8.8	1.5	0	0	0	
Li F [57]	2014	40	NR	NR	1.25	2.5	32.5	15.0	7.5	2.5	0	
(b) Series including open and laparoscopic colectomy and ileorectal anastomosis												
Zutshi [48]	2007	69	NR	10.0	1.4	7.2	17.4	16.0	1.4	1.4	0	
Riss [52]	2009	20	190	10.5	5.0	35.0	45.0	5.0	15.0	5.0	15.0	
Reshef [†] [56]	2013	144	NR	7.8	3.5	17.0	54.0	26.0	14.0	6.9	1.0	
Dudekula [19]	2015	2377	NR	8.0	NR	NR	42.7	27.0 [¶]	NR	NR	NR	
(c) Laparoscopic colectomy and ileorectal anastomosis												
Ho [34]	1997	7	NR**	9.2	NR	14	43.0	29	0	0	0	
Xu [20]	2008	44	197	7.6	NR	4.5	18.2	11.4	4.5	2.3	0	
Pinedo [51]	2009	20	248	7.0	10.0	NR	NR	15.0	5.0	5.0	0	
Xu [20]	2012	32	122	8.5	NR	NR	NR	0	3.1	3.1	0	
Wang [55]	2013	56	223	8.7	0	5.3	7.1	1.8	0	0	0	
Author	Year	Operation	N	Time	LOS	Bleed	Inf	Total cx	POI*	Re-op	Leak	Mort
(d) Subtotal colectomy and ileosigmoid anastomosis (ISA); isoperistaltic caecorectal anastomosis (IPCCA); antiperistaltic caecorectal anastomosis (APCCA); lap: laparoscopic												
de Graaf [28]	1996	ISA	24	NR	NR	NR	NR	NR	NR	NR	NR	4.2
Feng [22]	2008	ISA	45	135	13.1	NR	NR	20	NR	0	0	0
Sun [58]	2015	ISA	22	NR	NR	NR	NR	NR	NR	NR	NR	0
Feng [22]	2008	IPCRA	34	120	12.5	NR	NR	NR	NR	0	0	0
Li F [57]	2014	IPCRA	32	NR	NR	0	3.1	28.1	12.5	3.1	3.1	0
Sun [58]	2015	IPCRA	26	NR	NR	NR	NR	NR	NR	NR	NR	0
Marchesi [47]	2007	APCRA (5 lap)	17	NR	11.9	NR	NR	9.3	5.9	11.8	5.9	0
Jiang [50]	2008	APCRA	17	130	14.5	NR	5.9	NR	NR	NR	0	0
Marchesi [54]	2012	APCRA	15	184	10.9	NR	NR	13.3	0	0	0	0
Marchesi [54]	2012	APCRA lap	15	232	9.3	NR	NR	13.3	0	0	6.7	0

Cx, complications; NR, not reported.

*Includes prolonged ileus and early mechanical obstruction.

†In patients with STC only.

‡70 min shorter than laparoscopic procedures in same series (actual duration not reported).

§5 patients had colectomy and end ileostomy.

¶Includes 'intestinal obstruction, POI, nausea and vomiting, and haemorrhage'. POI, postoperative ileus.

**+/- rectopexy.

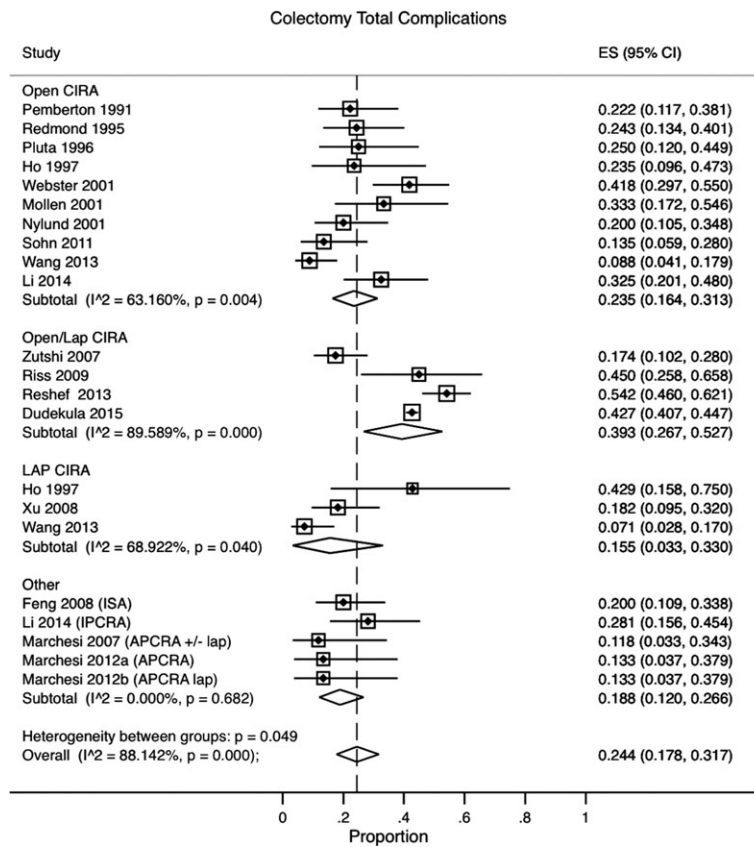


Figure 2 Forest plot showing total complications (percentage of patients) after colectomy by procedure type. CIRA, colectomy and ileorectal anastomosis; lap, laparoscopic; ISA, ileosigmoid anastomosis; IPCRA, isoperistaltic caecorectal anastomosis; APCRA, antiperistaltic caecorectal anastomosis.

problems) were similarly heterogeneous 13.3%, (95%CI: 8.6–18.7%) $I^2 = 87.7\%$, including study rates from 0% to 45% (Fig. 4b). Particular to colectomy for constipation is the concept that laparoscopy might reduce the well-established high incidence of post-operative SBO. The review provided only limited data from small studies comparing open with laparoscopic procedures, although SBO rates appeared much lower. Ho *et al.* [34] found that early adhesion formation leading to bowel obstruction was more frequent in patients undergoing laparoscopically assisted colectomy (29%) compared to open (13%). A larger series of 124 patients also showed no differences in post-operative morbidity between approaches [55]. Conversely, a low quality case-control study of 15 laparoscopic *vs* 15 open subtotal colectomy with antiperistaltic CRA showed that bowel obstruction rates were halved (from 13.3 to 6.7%) in the laparoscopic groups [54]. The follow up in these studies (12–20 months) was generally shorter than the average (47 months) although very high rates of SBO were reported by a study of exclusively open CIRA with 12 months follow up [52]. Finally, while the results for laparoscopic approach offer some optimism based on the small numbers of patients in these studies, no differences were observed in complication

rates between open and laparoscopic procedures in the US nationwide survey of 2377 colectomies [19].

However, the most revealing conclusions can be drawn from further analysis of US national database study in which longitudinal data were recorded on 166 patients recorded on State Inpatient Databases of Florida and California (2005–2011). These data agreed with the whole national dataset ($n = 2377$) in confirming high perioperative (30-day) complication and re-admission rates, but also showed that resource utilisation in the form of emergency department visits, hospitalisation and surgical intervention remained high in the following 1 year. Excluding the colectomy itself, these 166 patients had a total of 2355 encounters, which included 1494 emergency department visits and 861 hospitalisations by 149 and 144 patients, respectively. Among the 1494 emergency department visits, the 674 that occurred postoperatively were shared across 119 (72%) patients; among the 861 hospitalisations, 488 occurred after colectomy and affected 110 (66%) patients. A breakdown of the motivation for these attendances reveals the well-described issue of ongoing abdominal pain, which as well as other gastrointestinal symptoms and postoperative complications, increased after colectomy.

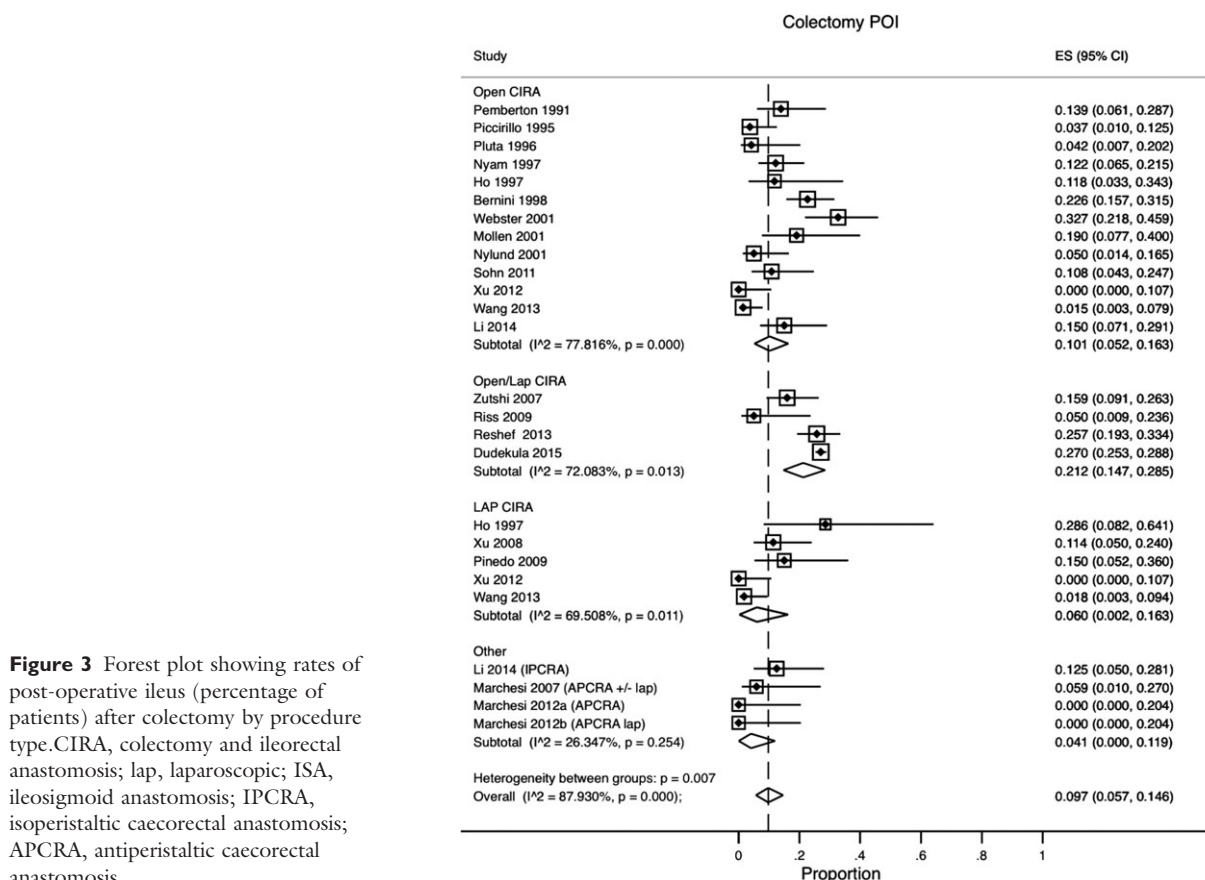


Figure 3 Forest plot showing rates of post-operative ileus (percentage of patients) after colectomy by procedure type. CIRA, colectomy and ileorectal anastomosis; lap, laparoscopic; ISA, ileosigmoid anastomosis; IPCRA, isoperistaltic caecorectal anastomosis; APCRA, antiperistaltic caecorectal anastomosis.

Summary evidence statements: harms

- 1 Data on harms were inconsistently reported and heterogeneous in findings, thus estimates of harm are tentative and imprecise (level IV).
- 2 Proportionally greater evidence for perioperative outcomes comes from studies of colectomy and ileorectal anastomosis than for other procedural variations (CIRA: 29 studies, 1321 patients; other procedures: 10 studies, 247 patients) (level IV).
- 3 Total perioperative complication rates vary greatly but may occur in approximately 20–30% of colectomy patients. The influence of resection extent, anastomotic configuration and method of access on complication rates remains uncertain (level IV).
- 4 Rates of post-operative ileus or early post-operative adhesional small bowel obstruction vary greatly but may occur in about 5–15% of patients and about one third of these patients require re-operation (level IV).
- 5 Mortality rate for 39 studies reporting this outcome was 6 / 1568 patients (0.4%) (level IV).
- 6 Long-term adverse events characterized by recurrent episodes of small bowel obstruction occur in about

10–20% of patients and may result in a significant burden of re-hospitalization and frequent recourse to surgery in most of these patients (level IV).

- 7 Current evidence tentatively suggests laparoscopic surgery may reduce some complications when compared to open surgery, although this needs to be confirmed by better designed studies (level IV).

Efficacy

Measurement of outcome was inconsistent, including variable use of validated and un-validated scoring instruments for symptoms e.g. Cleveland Clinic Constipation Score or quality of life (QoL), GI quality of life, individual symptom reporting and global 'success' or 'satisfaction' ratings (GSR) obtained via a variety of methods (where 'satisfied' or 'very satisfied', 'good', 'very good' and 'excellent' were interpreted as positive outcomes). No study documented that data were acquired objectively by using personnel not involved in the surgical care of the patient. Only one study documented that collection of data was blind to intervention status [20] and this RCT only blinded observers for 4 days while presenting follow up data to 32 months. Average

Table 3 Long-term small bowel obstruction and re-operation rates.

Author	Year	Operation	N	SBO	Re-operation*
(a) Open colectomy and ileorectal anastomosis					
Pemberton [26]	1991	CIRA	36	11.1	8.3
Piccirillo [27]	1995	CIRA	54	9.3	3.7
Redmond [21]	1995	CIRA	37	18.0	NR
Lubowski [29]	1996	CIRA	52	17.0	14.0
Pluta [31]	1996	CIRA	24	21.0	8.4
Ghosh [32]	1996	CIRA	21	71.0	42.0
Nyam [33]	1997	CIRA	74	9.5	6.7
Bernini [36]	1998	CIRA	106	29.0	18.0
Pikarsky [39]	2001	CIRA	62	7.3 (21.4) [†]	2.4 (14.3) [†]
Pikarsky [40]	2001	CIRA	30	20.0	10.0
Mollen [42]	2001	CIRA	21	19.0	9.5
Nylund [43]	2001	CIRA	40	42.5	42.5
Fitzharris [45]	2003	CIRA	75	38.0	17.0
Hassan [46]	2006	CIRA	65	0	0
Jiang [50]	2008	CIRA	21	15.0	NR
Sohn [53]	2011	CIRA	37	10.8	2.7
Wang [55]	2013	CIRA	68	2.9	0
Kamm [23]	1988	Mix	44	NR	38.0
Vasilevsky [24]	1988	Mix	52	36.0	24.0
Yoshioka & Keighley [25]	1989	Mix	40	NR	30.0
Platell [30]	1996	Mix	96	10.4	36.0
Hasegawa [37]	1998	Mix	61	NR	45.0
Fan [38]	2000	Mix	24	21.0	4.2
de Graaf [28]	1996	Segmental on transit	42	2.0	2.0
You [35]	1998	Segmental on transit	40	NR	7.5
Lundin [44]	2002	Segmental on transit	28	19.2	25.0
Feng [22]	2008	IPCRA	34	8.9	NR
Feng [22]	2008	ISA	45	6.7	NR
Jiang [50]	2008	APCRA	17	11.8	NR
Marchesi [54]	2012	APCRA	15	13.3	13.3
(b) Series including open and laparoscopic procedures					
Marchesi [47]	2007	APCRA	23	5.9	11.8
Zutshi [48]	2007	CIRA	69	20.0	11.6
Riss [52]	2009	CIRA	20	65.0	45.0
Reshef [56]	2013	CIRA	144	NR	20.0
Dudekula [19]	2015	CIRA	56	NR	30 additional surgeries in 12 months F up
(c) Laparoscopic procedures only					
Pinedo [51]	2009	APCRA	20	5.0	5.0
Marchesi [54]	2012	APCRA	15	6.7	0
Wang [55]	2013	CIRA	56	0	0

SBO, small bowel obstruction; NR, not reported.

*Includes all reported for bowel complications although majority are for adhesional SBO.

[†](Values) for age 65–85 years.

reported follow-up of studies was 4.3 years (range 1–11 years).

Accepting these methodological limitations, there are many reports supporting the assertion that most patients undergoing colectomy are satisfied; meta-analysis of

studies found an overall global satisfaction rating of 85.6% (95%CI: 81.4–89.3%), $I^2 = 76.9\%$ based on data from 1616 patients (Table 4; Fig. 5). Again study findings are heterogeneous, with no clear advantage for any particular procedure or surgical approach. However, such

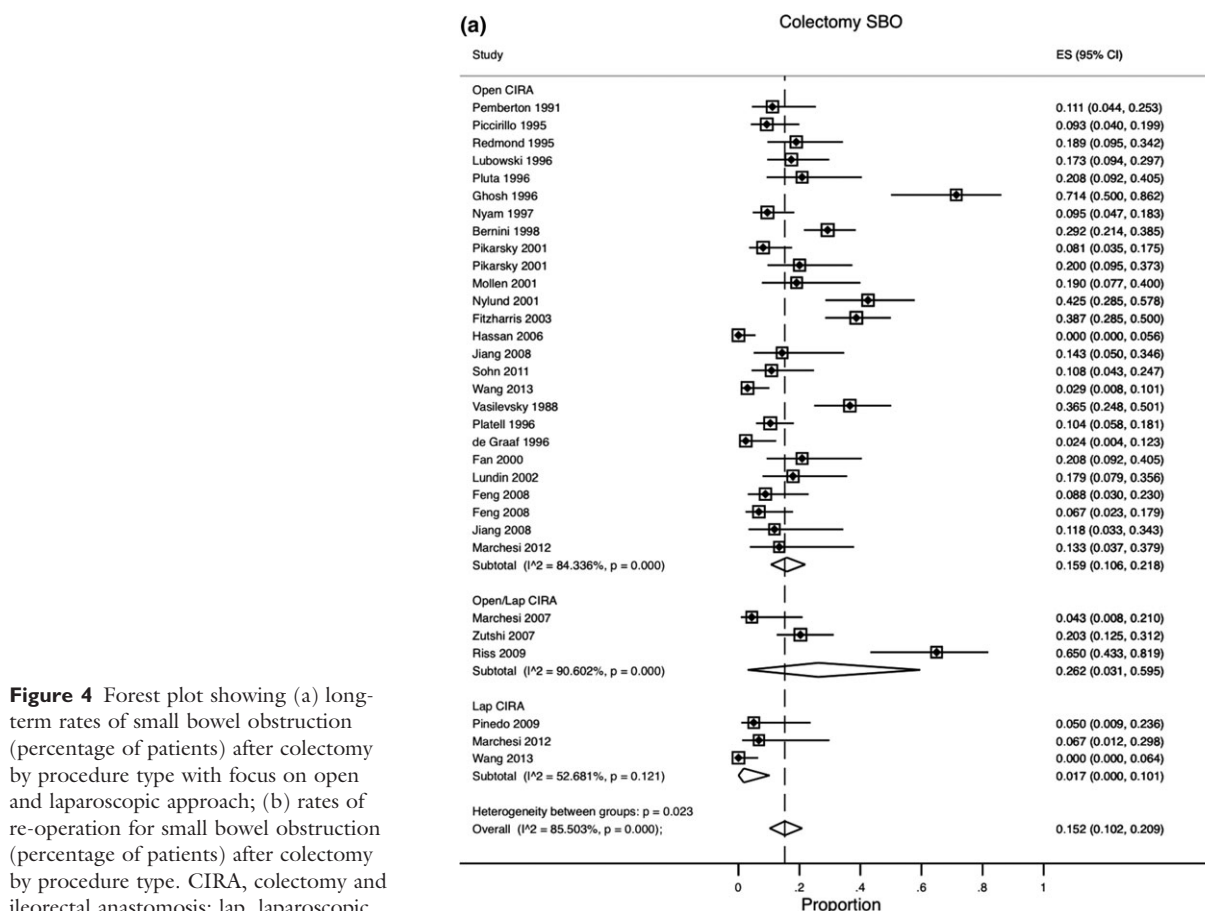


Figure 4 Forest plot showing (a) long-term rates of small bowel obstruction (percentage of patients) after colectomy by procedure type with focus on open and laparoscopic approach; (b) rates of re-operation for small bowel obstruction (percentage of patients) after colectomy by procedure type. CIRA, colectomy and ileorectal anastomosis; lap, laparoscopic.

levels of satisfaction can be related to marked changes in bowel frequency (generally from a mean of once per week to three times per day in the 14 studies reporting both variables) (Table 5), and where recorded (three studies only), marked changes in summative symptom scores e.g. the Cleveland Clinic Constipation score reduced from a mean of > 20 points pre-operatively (indicative of severe constipation) to approx. 2–3 points (low normal range) post-operatively. Individual symptom outcomes highlighted the well documented problems of diarrhoea: 9.8% (95%CI: 4.7–16.4%), $I^2 = 76.9\%$ (Fig. 6); and incontinence: 7.4%, (95%CI: 2.2–14.7%), $I^2 = 90.8\%$ following colectomy, ongoing or recurrent constipation: 18.2%, (95%CI: 9.3–29.2%), $I^2 = 91.4\%$; persistent (or worsened) abdominal pain: 39.3%, (95%CI: 28.8–50.1%), $I^2 = 89.0\%$; and bloating 23.9%, (95%CI: 11.9–38.1%), $I^2 = 92.7\%$. Poor functional outcomes contributed to further resection or permanent stoma: median 5% (range 0–28%) patients when reported (by only seven studies; data not shown).

Meta-analyses of efficacy outcomes featured considerable heterogeneity, not explained by procedure or age

of publication. Given the different duration of studies and variable follow up within studies there is also the potential for time-confounding. Studies limited only to laparoscopic procedures are characterized by small numbers limiting scope for comparison with open procedures and no adjustment has been attempted for potential differences in the populations recruited into individual studies. Consequently efficacy estimates are tentative.

Accepting the caveat that only a minority of studies reported functional variables, several observations can be made regarding functional outcomes in studies of less radical colonic resections (Tables 5b and c) compared to those for CIRA (Table 5a). The general premise of such procedures is to reduce the risk of long-term diarrhoea and incontinence and this concept is in part supported by data that, accepting small study numbers and heterogeneity, suggest potential to reduce rates of diarrhoea for segmental and subtotal resections (Fig. 6). However, this was at the cost of increased ongoing or recurrent constipation (median 8.7% for CIRA compared to 26.8% for more conservative

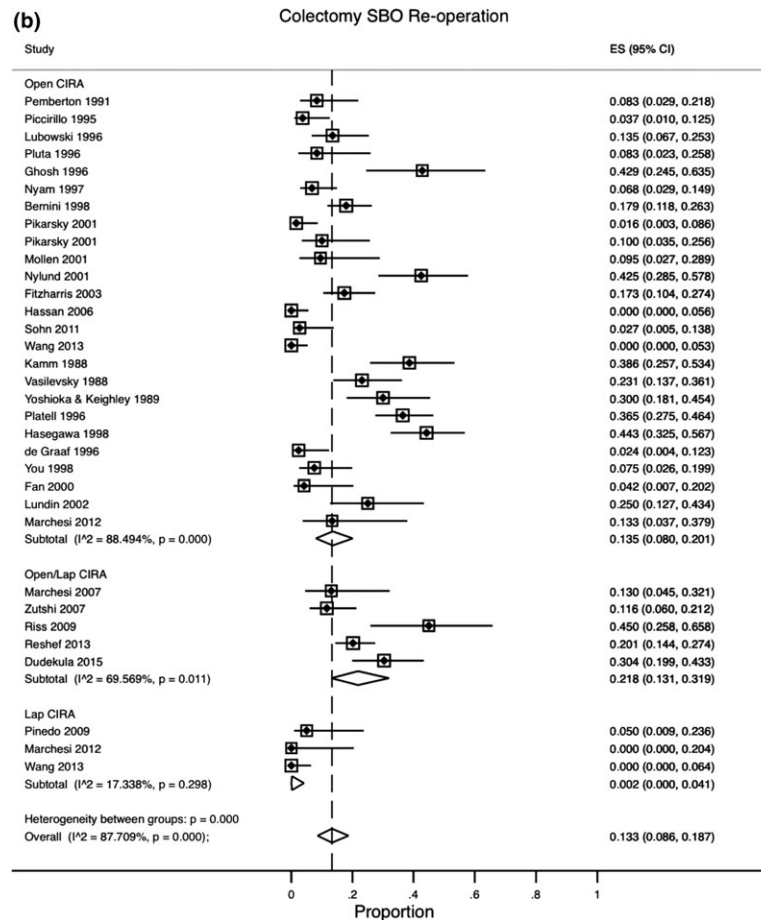


Figure 4 Continued

resections). The latter has proved a particular problem for segmental resections (right or left hemicolectomy) with generally poor results compared to colectomy mainly due to unresolved constipation requiring further intervention (Table 5c). De Graaf *et al.* [28] used segmental transit (radio-opaque marker) methodology to select patients for partial left sided colectomy or subtotal colectomy. Whilst results as a whole were disappointing, the study concluded that in terms of complications and functional outcome, there was little difference between procedures, and that a more limited resection was therefore a reasonable option in this selected group. You *et al.* [35] reported the use of left, right or subtotal colectomy based on segmental transit time measurements with excellent results. Further, in the three cases where constipation recurred following segmental resection, a subtotal colectomy was undertaken successfully at a later date. This experience was not however repeated by Lundin *et al.*, [44] when recurrent constipation was experienced by 46% patients despite transit-guided resection. Thus, while in the laparoscopic era

where there is a greater theoretical advantage of not meeting the technical challenges of mobilizing both colonic flexures laparoscopically, the tailoring of segmental resections using these specialist investigations of transit is inconsistently supported by published data. Further, the tests required to accurately determine resection level e.g. isotope scintigraphy have limited availability.

Subtotal resection with ileosigmoid anastomosis is generally considered less effective than ileorectal anastomosis based on several relatively small case series mixing both procedures (Table 4d). Contemporary data on subtotal resections with CRA come mainly from a few institutions in Italy and China. Conclusions from these studies vary. For example, Li *et al.* [57] demonstrated good results for both isoperistaltic CRA and CIRA. Feng *et al.* [22] compared isoperistaltic CRA with SCISA. Surgical safety outcomes and length of stay were similar but patients were more satisfied after ileosigmoid anastomosis mainly due to ongoing constipation in caecorectal group. However patients experienced slightly less

Table 4 Percentage success based on global satisfaction ratings (GSR).

Author	Year	FU (mean)	Operation	N	% success
(a) Colectomy and ileorectal anastomosis					
Pemberton [26]	1991	36	Open	36	100
Piccirillo [27]	1995	27	Open +/- rectopexy	54	94
Redmond [21]	1995	90	Open	34	90*
Lubowski [29]	1996	42	Open	52	90
Pluta [31]	1996	65	Open	24	92
Nyam [33]	1997	56	Open	74	97
Ho [34]	1997	24	Open	17	96
Ho [34]	1997	24	Laparoscopic	7	100
Bernini [36]	1998	78	Open	106	78†
Fan [38]	2000	23	Open‡	24	88
Pikarsky [40]	2001	60	Open	30	100
Webster & Dayton [41]	2001	12	Open (5 ileostomy)	55	89
Mollen [42]	2001	62	Open	21	76
Nylund [43]	2001	132	Open	40	73
Fitzharris [45]	2003	47	Open	75	69
Hassan [46]	2006	68	Open	65	85
Zutshi [48]	2007	130	Open & laparoscopic (n = 7)	69	79
Jiang [50]	2008	48	Open	21	65
Hsiao [49]	2008	12	Laparoscopic	44	89
Sohn [53]	2011	41	Open	37	84
Reshef [56]	2013	43	Open & laparoscopic (n = 7)	144	89§
Li [57]	2014	64	Open	40	93
(b) Subtotal colectomy and ileosigmoid anastomosis (ISA); isoperistaltic caecorectal anastomosis (IPCRA); antiperistaltic caecorectal anastomosis (APCRA); lap: laparoscopic					
de Graaf [28]	1996	46	ISA	24	67
Feng [22]	2008	47	ISA	45	93
Marchesi [47]	2007	72	APCRA (lap n = 5)	17	88
Jiang [50]	2008	48	APCRA	17	88
Feng [22]	2008	47	IPCRA	34	74
Li [57]	2014	33	IPCRA	32	97
(c) Segmental colectomy (all based on regional transit measurement)					
de Graaf [28]	1996	46	Lt hemicolectomy	18	62.5
You [35]	1998	24	Segmental based on transit	40	92
Lundin [44]	2002	50	Segmental based on transit¶	28	86
(d) Mixed procedures					
Kamm [23]	1988	> 12	CIRA / IPCRA (11)	44	50
Vasilevsky [24]	1988	46	CIRA (5) / ISA	51	79
Yoshioka & Keighley [25]	1989	36	CIRA / ISA (1) / IPCRA (5)	40	58
Platell [30]	1996	60	CIRA / IPCRA (10)	96	81.3
Hasegawa [37]	1999	84	CIRA, ISA, IPCRA, segmental	61	39–95**

FU, mean follow up in months; NR, not reported.

*12.5% with generalized intestinal disorder (see text).

†56% with associated rectal evacuatory disorder.

‡2 patients had caecorectal anastomosis.

§85% with associated rectal evacuatory disorder.

¶26 of 28 had left hemicolectomy (6 with rectopexy) and 2 right.

**Outcome dependent on psychiatric disease and concomitant rectal evacuation disorder.

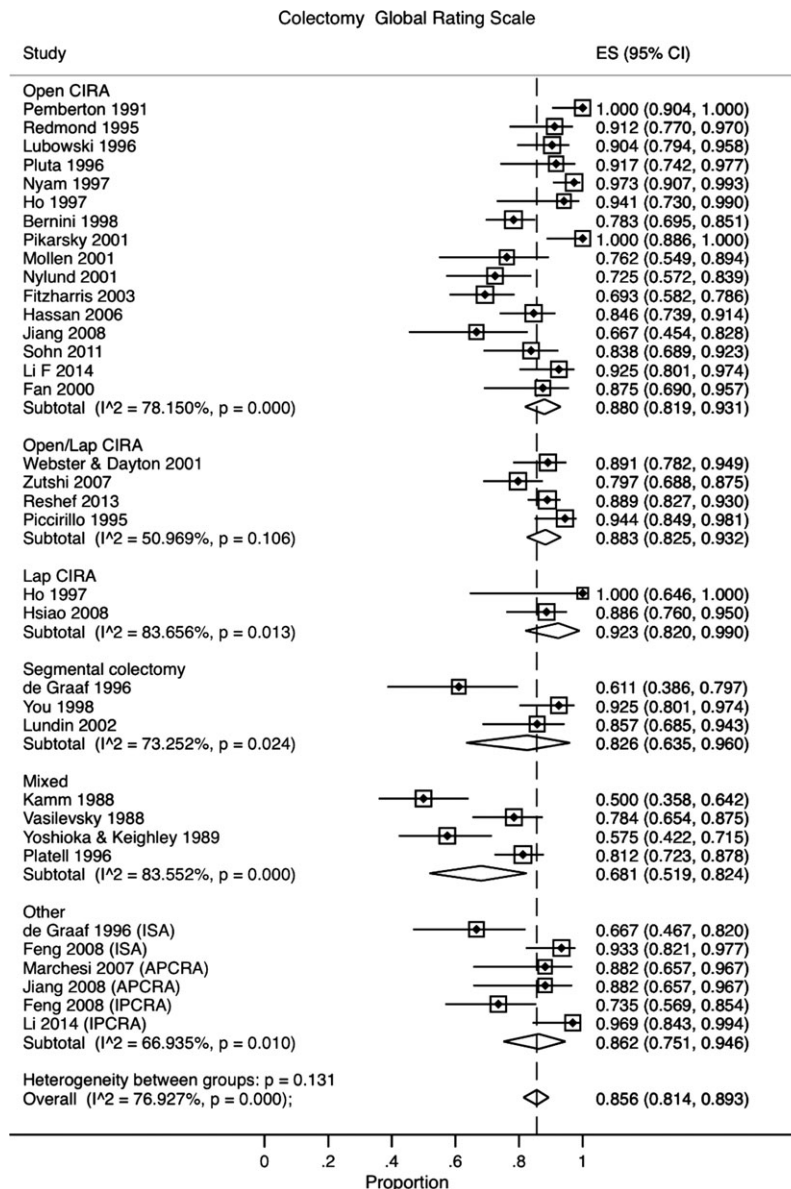


Figure 5 Forest plot showing global success rates as defined by percentage of patients who were 'satisfied' or 'very satisfied' with outcome, or where outcome was defined as 'good' or 'excellent' after colectomy by procedure type. CIRA, colectomy and ileorectal anastomosis; lap, laparoscopic; ISA, ileosigmoid anastomosis; IPCRA, isoperistaltic caecorectal anastomosis; APCRA, antiperistaltic caecorectal anastomosis; mixed, mix of resection types reported in each case series.

diarrhoea and incontinence after caecorectal anastomosis. Jiang *et al.* [50] compared antiperistaltic CRA with ileorectal anastomosis. Again there were no differences in post-operative course, however patients undergoing caecorectal anastomosis had less diarrhoea, higher post-operative quality of life (not recorded pre-operatively) and overall reported GSR (88 *vs* 65%).

Laparoscopic surgery has the theoretical advantages of better cosmesis (especially in young women) and perhaps lower long-term complication rates (see above). Such factors have not however yet translated into improved functional outcomes mainly because these have not yet been the focus of comparative studies. Ho *et al.* [34] found no difference in GSR between open

and laparoscopic CIRA (96 *vs* 100%). In the case-control study of Marchesi *et al.* [54], despite the halving of SBO rates (from 13.3 to 6.7%) in the laparoscopic groups, long-term functional outcomes and GI quality of life were very similar.

Summary evidence statements: efficacy

- 1 Proportionally greater evidence for efficacy comes from studies of colectomy and ileorectal anastomosis than for other procedural variations (CIRA: 25 studies, 1209 patients; mixed: 5 studies, 280 patients; other procedures: 9 studies, 247 patients; and segmental procedures 4 studies, 99 patients (level IV)).

Table 5 Functional outcomes by procedure.

Author	Year	Procedure	N	BF pre	BF post	CCS pre	CCS post	D	I	AP	L	B	RC
(a) Colectomy and ileorectal anastomosis													
Pemberton [26]	1991	Open	36	NR	14.0	NR	NR	0	0	NR	0	0	0
Redmond [21]	1995	Open	37	NR	26/5*	NR	NR	NR	NR	0/69*	0/44*	0/44*	NR
Piccirillo [27]	1995	Open†	54	NR	26	NR	NR	24	24	NR	1.9	NR	NR
Lubowski [29]	1996	Open	52	NR	28.0	NR	NR	14	12	52	NR	NR	26.9
Pluta [31]	1996	Open	24	1.4	18.0	NR	NR	33	NR	58	NR	29	NR
Ghosh [32]	1996	Open*	21	NR	NR	NR	NR	NR	NR	90	NR	NR	NR
Nyam [33]	1997	Open	74	NR	28 §14	NR	NR	< 10	1	NR	2 §9	NR	0
Ho [34]	1997	Open	17	0.3 ∞ 1.2	17 ∞ 15.4	NR	NR	0	0	NR	0	0	0
Bernini [36]	1998	Open	90	NR	19.6 §14.6 DD	NR	NR	14 §15	21 §20	44 §37	NR	45 §43	4 §38
Fan [38]	2000	Open	24	1.4	22.8	NR	NR	8.3	0	NR	8.3**	NR	8.3**
Pikarsky [39]	2001	Open	62	1.4 †† 1.0	20.3 †† 26.6	NR	NR	9 †† 27	17 †† 36	NR	0 †† 9	NR	NR
Pikarsky [40]	2001	Open	30	NR	17.5	NR	NR	NR	17	NR	6	23	NR
Webster & Dayton [41]	2001	Open**	55	NR	21.0	NR	NR	5	4	19	NR	10	9
Mollen [42]	2001	Open	21	0.8	19.6	NR	NR	NR	10	86	62	90	76
Nylund [43]	2001	Open	40	1.1	3.8	NR	NR	NR	7.5	38	NR	NR	NR
Fitzharris [45]	2003	Open	75	NR	2.5	NR	NR	25	45	41	20	NR	NR
Zutshi [30]	2007	Open & lap	69	1.0	21.0	NR	NR	NR	NR	37	NR	66	51
Jiang [50]	2008	Open	21	1.4	23.8	NR	NR	15	NR	20	NR	25	NR
Pinedo [51]	2009	Lap	20	NR	NR	22.3	1.8	NR	NR	5	NR	NR	5
Riss [52]	2009	Open or lap	20	NR	NR	NR	11.5 §§	NR	NR	NR	NR	NR	50 §§
Sohn [53]	2011	Open	37	NR	NR	19.3	2.1	NR	NR	NR	NR	NR	NR
Xu [20]	2012	Open	32	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang [55]	2013	Open or lap	114	NR	35.0	NR	NR	NR	NR	NR	6	NR	6
Reshef [56]	2013	Open or lap	144	NR	31.0 (33.0)	NR	NR	NR	11 (15)	31 (33)	13 (26)	NR	NR
Li [57]	2014	Open	40	NR	NR	27.3	NR	2.5	2.5	13	NR	7.5	NR
(b) Subtotal colectomy and ileosigmoid anastomosis (ISA); isoperistaltic caecorectal anastomosis (IPCRA); and antiperistaltic caecorectal anastomosis (APCRA); lap: laparoscopic													
de Graaf [28]	1996	ISA	24	NR	NR	NR	NR	12.5	8.3	62.5	20.8	50	29.2
Feng [22]	2008	ISA	45	1.6	15.5	NR	NR	4.5	2.2	17.8	6.7	15.6	6.7
Sun [58]	2015	ISA	22	1.1	34.3	NR	5	NR	NR	NR	NR	NR	NR
Marchesi [47]	2007	APCRA	17	NR	19.6	20.3	2.6	NR	NR	NR	NR	NR	NR
Feng [22]	2008	IPCRA	34	1.5	10.2	NR	NR	NR	0	24	26.8	24	26.8
Jiang [50]	2008	APCRA	17	1.5	16.8	NR	NR	0	NR	NR	NR	23.5	NR
Marchesi [54]	2012	APCRA	30	NR	18.2	20	3	NR	NR	NR	NR	NR	NR
Li [57]	2014	IPCCRA	32	NR	NR	27	NR	3.1	0	3.1	NR	3.1	NR

Table 5 (Continued).

Author	Year	Procedure	N	BF pre	BF post	CCS pre	CCS post	D	I	AP	L	B	RC
Sun [58]	2015	IPCCRA	26	1.1	16.1	NR	3.2	NR	NR	NR	NR	NR	NR
(c) Segmental colectomy													
de Graaf [28]	1996	Lt hemicolectomy on transit	18	NR	NR	NR	NR	5.6	5.6	33.3	16.7	22.2	16.7
You [35]	1998	Segmental on transit	40	1	14	NR	NR	0	NR	NR	NR	0	8
Hasegawa [37]	1999	Segmental mix	13	NR	NR	NR	NR	NR	NR	NR	NR	NR	62
Lundin [44]	2002	Predom. left hemi on transit	28	1	7	NR	NR	NR	NR	50	0	67	46
(d) Mixed procedures													
Kamm [23]	1988	IRA / APCRA	44	NR	NR	NR	NR	39	14	71	45	45	11
Vasilevsky [24]	1988	IRA / ISA (predom)	52	NR	19.6	NR	NR	NR	2	NR	20	NR	NR
Yoshioka & Keighley [25]	1989	IRA / ISA / IPCRA	40	0.3	21.0	NR	NR	33	NR	39	NR	NR	NR
Platell [30]	1996	IRA / IPCRA	96	NR	NR	NR	NR	NR	52	55	NR	NR	NR
Hasegawa [37]	1999	IRA, ISA, IPCRA	48	NR	NR	NR	NR	NR	NR	NR	NR	NR	33

NR, not reported; BF, Bowel frequency/week; CCS, Cleveland Clinic Constipation score; D, diarrhoea; I, incontinence; AP, abdominal pain; L, laxatives; B, bloating; RC, recurrent constipation.

*If associated generalized intestinal disorder (GID).

[†]5 with rectopexy.

[‡]Includes one segmental resection.

[§]Values if STC associated with concomitant RED; values for laparoscopic where these differed.

^{**}In 2/24 patients undergoing caecorectal anastomosis.

^{††}Age 65–80 (compared to 21–61 years).

^{‡‡}Includes one end ileostomy.

^{§§}Based on 12 patients in follow up.

Studies not reporting a cohort average, i.e. only subgroups were excluded from the meta-analysis.

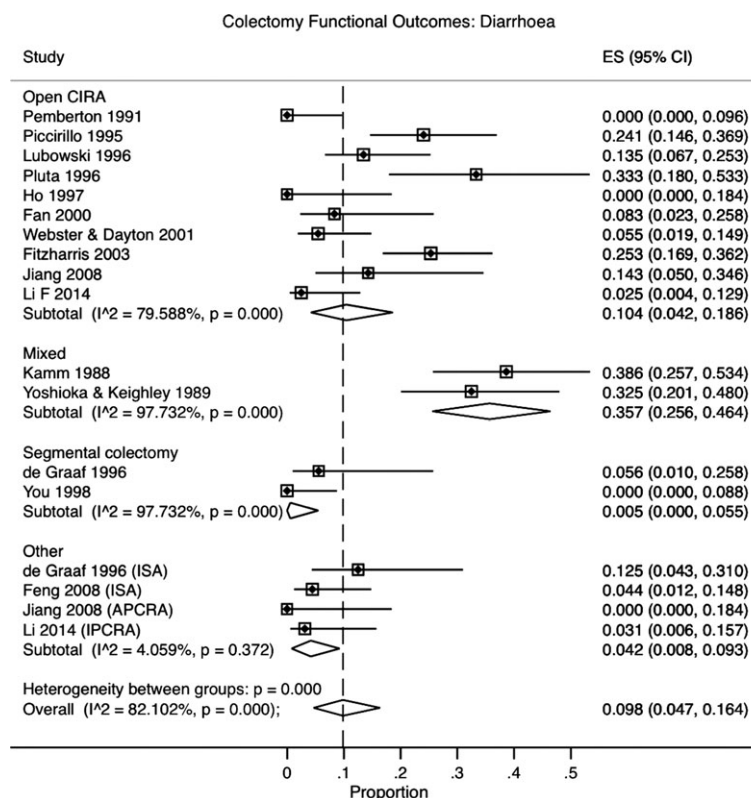


Figure 6 Forest plot showing rates of long-term diarrhoea (percentage of patients) after colectomy by procedure type. CIRA, colectomy and ileorectal anastomosis; lap, laparoscopic; ISA, ileosigmoid anastomosis; IPCRA, isoperistaltic caecorectal anastomosis; APCRA, antiperistaltic caecorectal anastomosis; mixed, mix of resection types reported in each case series.

- Data on efficacy were inconsistently reported and heterogeneous in findings, thus estimates were tentative and imprecise. Studies varied in their follow-up of patients, the mean follow-up in studies was 4.3 years (range 1–11 years) (level IV).
- Colectomy (based on the global rating of success) benefits the majority of patients with slow transit constipation: overall mean 85.6% (95% CI: 81.4–89.3%) at > 12 months follow up (level IV).
- Negative long term functional outcomes persist in a minority of patients: diarrhoea and incontinence in about 5–15% of patients; abdominal pain in 30–50% of patients; recurrent constipation in 10–30% of patients and bloating in 10–40% (level IV).
- Tailoring of segmental resections using specialist regional transit measurements provides uncertain benefit (level IV).
- There are insufficient data to conclude: (a) that alternative procedures (subtotal or segmental) perform better than CIRA; (b) that one type of subtotal resection (caecorectal *vs* ileosigmoid) or anastomosis (iso- or anti-peristaltic) is superior to another; (c) that laparoscopic approach has benefit over open surgery (level IV).
- Subtotal colectomy may reduce long-term rates of diarrhoea compared to CIRA although this finding is

tentative and should be verified with better designed studies (level IV).

Patient selection

While clinical experience suggests careful patient selection for procedures is important, few studies systematically addressed this issue [12]. Main findings from studies that stratified outcomes based on baseline phenotype are included in Table 6. These studies provide some information on clinical characteristics but more so on results of specialist physiological testing.

Pikarsky *et al.* [39] studied whether colectomy can be performed in elderly patients (defined 65–80 years in their series). Although overall success was diminished on the older age group (64% *vs* 95%, $P = 0.01$), the authors concluded that the results were acceptable and that the procedure was safe based on no increase in observed morbidity. The question of whether the presence of severe psychological problems adversely influences outcome has been discussed by studies that noted both poor outcomes and a number of post-operative psychological problems including suicide [23]. Others have made post-hoc correlations between prior psychiatric disease and poor outcome [31]. This factor was only addressed as a stated aim by Hasegawa *et al.* [37], who

Table 6 Summary of prognostic findings.

Author	Year	Factor studied	Op	N	FU	Main findings: perioperative	Main findings: functional	Main findings: long-term morbidity
Redmond [21]	1995	GID	CIRA	34	90	Increased perioperative morbidity (44% <i>vs</i> 24%) with GID and increased LOS: 13.1 <i>vs</i> 12.1 days	GRA 12.5% <i>vs</i> 90% satisfied with outcome in GID group; at 2 years: BH 5 <i>vs</i> 28 p.w. rec. constipation & pain 56% in GID <i>vs</i> 5% in no GID group. Similar findings for bloating, abdominal pain and laxative requirements at 2 years and worse at 5 years	1 death in both groups: GID secondary to TPN catheter
Nyam [33]	1997	RED	CIRA	74	56	NR	Results similar (no s.d) between RED and no RED for all studied	NR
Hasegawa [37]	1999	RED & psych	Mix	61	84	NR	Failure in 11% without <i>vs</i> 39% with RED; failure in 70% with psychological problems (inc s-fold increase in admissions, further surgery, and 5 fold increase in eventual stoma)	
Bernini [36]	1998	RED	CIRA	106	78	NR	GRA decreased if RED: 56 <i>vs</i> 78%; weekly BF 14.7 <i>vs</i> 19.6; no diff in other symptoms	SBO only in CI group - 23 <i>vs</i> 0%
Pikarsky [39]	2001	Age < or > 65 years	CIRA	59	105	SBO 21% in age over 65 <i>vs</i> 7% in younger patient group	Weekly BF higher (n.s) in older group (26.6 <i>vs</i> 20.3); excellent outcome in 64% older <i>vs</i> 95%; increased FI in older (36% <i>vs</i> 17%)	1/14 older group required stoma
Hassan [46]	2006	RED	CIRA	104	68	NR	No diff in KESS and SF-12 with or without RED	No diff in ileostomy rates (5% both groups)
Reshef [56]	2013	RED	CIRA	144	43	LOS longer with RED 9.7 <i>vs</i> 7.8 days; overall morbidity otherwise similar 61 <i>vs</i> 54% POI; re-operation 41 <i>vs</i> 26%	Inc. lax use in RED group (26 <i>vs</i> 13%) other variables similar inc. overall satisfaction: GRA 89 <i>vs</i> 85	or re-admissions (30% both groups)

RED, rectal evacuation disorder; GID, generalized intestinal disorder; BF, biofeedback; CIRA, colectomy and ileorectal anastomosis; KESS, Knowles-Ecclesley-Scott score; LOS, length of stay.

reported a statistically significant prejudicial influence of 'severe psychological disorder'.

Outcomes of colectomy are improved by selection of patients with proof of slow colonic transit. Although it could be argued that other factors may have also influenced outcomes (e.g. mix of surgical approaches, surgical technique and equipment), this statement is corroborated by comparing outcome data from an era when specialist investigations of transit were variably applied [23–25,37] with subsequent studies that always performed transit studies and used these as a selection criteria. Most contemporary studies also evaluated anorectal physiology especially in relation to the diagnosis of a combined slow-transit and defaecatory disorder phenotype. The management of this patient group remains contentious. Bernini *et al.* [36] in a study of 106 patients demonstrated that despite preoperative biofeedback training, patients with non-relaxing pelvic floor ($n = 16$) had significantly higher rates of recurrent defaecatory difficulty (38 *vs* 4%), and lower rates of satisfaction after colectomy (56 *vs* 78%). However, three other studies (Table 6) found little effect on functional outcome or complication rates when functional or structural defects were addressed prior to colectomy. These studies included the contemporary Cleveland Clinic experience of 144 patients where obstructed defaecation ($n = 41$) had no influence on outcome from laparoscopic or open colectomy [56].

It is generally accepted that some patients with slow colonic transit also manifest upper GI symptoms (especially nausea and vomiting). Abnormalities of oesophageal, gastric and small bowel function can be demonstrated in a proportion of patients by a variety of methods [18]. Ghosh *et al.* [32] showed that the high proportion of patients undergoing colectomy who subsequently developed SBO episodes (71% with 42% requiring surgery in their series) were more likely to have non-colonic visceral and autonomic nervous system abnormalities on post-operative testing. This observation has been considerably strengthened by the prospective cohort study of Redmond *et al.* [21]. A significant fall in long-term success rate (to 10 years) as a result of persistent constipation, abdominal pain and distension) was observed in patients defined as having a generalized intestinal disorder (GID) on the basis of having both upper and lower GI dysmotility using a battery of intraluminal tests. Successful outcome was observed in only 12.5% patients with GID *vs* 90% without.

Summary evidence statements: patient selection

- 1 Outcomes of colectomy may be poorer in patients with significant psychological disorder (level IV).

- 2 Outcomes of colectomy may be improved by selection of patients with definitive proof of slow colonic transit (level IV).
- 3 Outcomes of colectomy are inconsistently influenced by concomitant rectal evacuation disorder although data suggest that structural and functional defecation disorders, if evident, should be treated prior to colectomy (level IV).
- 4 Outcomes of colectomy may be prejudiced by pre-operative evidence of upper gastrointestinal dysmotility (level IV).

Conclusions

A systematic review of evidence for the perioperative and long-term benefits and harms of colectomy identified no high quality studies. The evidence base is characterised by observational studies of variable and often uncertain methodological quality. Current data suggest a balance of harms against efficacy with evidence that outcomes are at best variable. Future studies should provide high quality evidence for clinicians to support patient decision making, both in terms of the incremental benefits and harms of colectomy and in understanding the effects of prognostic factors upon treatment success.

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Conflict of interest

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